Facts and ideas from anywhere

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EVALUATING LIPID-LOWERING TRIALS IN THE 21ST CENTURY

It's these large multicenter, double-blind, often placebo-controlled clinical trials that have the greatest impact on how medicine now is practiced. With lipid-lowering drugs, the trials are of two basic types: 1) the outcome trials, listed in *Table 1* (1–11), and 2) the imaging trials, listed in *Table 2* (12–17).

To evaluate these trials appropriately, it is important to know the number of subjects and/or patients in the trial; their ages and gender; whether or not there was preexisting cardiovascular disease, diabetes mellitus, renal disease, valvular heart disease, or none of these; the length of the study; whether the study was or was not stopped early; whether the study drug was compared to placebo or to another drug or simply to a lower dose of the same drug; the doses of the drug or drugs studied; the endpoints of the trial; the percentage of events (in outcome trials) in both the study and control groups; the absolute and relative difference in percentage of events between groups at the end of the study period; and the baseline and final serum lipid values in the study patients and in the controls.

The outcome trials usually involve several thousand patients who are followed usually for 2 to 5 years and have primary endpoints that usually include various combinations of cardiovascular death, all-cause death, nonfatal acute myocardial infarction, stroke, hospitalization for unstable angina pectoris, and revascularization (percutaneous coronary intervention, coronary artery bypass grafting, and/or peripheral arterial procedures). These trials are usually very expensive and are usually sponsored by a single pharmaceutical company. At least 11 major outcome trials have been published during the present decade (Table 1).

In contrast to the outcome trials, the imaging trials (Table 2) involve far fewer patients (usually <1000) followed for a far shorter time period, and, as a consequence, they are far less expensive. Those reported have focused on the coronary artery (intravascular ultrasonic imaging [IVUS]) or on the carotid artery (intimal medial thickness [IMT]) and the change in plaque volume (IVUS) or millimeters (IMT) from baseline to the end of the trial.

The initial-result reports of the major lipid-lowering trials are usually published in the major general medicine journals. Each of the 17 trials briefly summarized in tables were published in *The New England Journal of Medicine* (seven trials), the *Journal of the American Medical Association* (six trials), or the *Lancet* (four trials). Because these journals are provided to the press shortly before publication, the results of these major trials appear in the media across the country, and many physicians first learn of the trials through the media. Most media reports of trials focus on the single trial whose results have just appeared and do not give the necessary perspective of the new trial's results compared with similar previous trial publications. And it is crucial not to draw absolute conclusions from single trials!

Three trials in recent times have received particular, in my view, unwarranted attention. One was the ENHANCE trial, an imaging (carotid IMT) trial comparing simvastatin (S) 80 mg + ezetimibe (E) 10 mg vs S80 mg in 720 patients followed a mean of 2 years after baseline IMT study (16). All patients had at baseline a low-density lipoprotein (LDL) cholesterol level >300 mg/dL. (Most physicians do not have a single patient in their practice with a baseline LDL cholesterol level that high!) The LDL cholesterol in the S80 + E10 group fell from 319 to 141 mg/dL (56%↓) and in the S80 group, from 318 to 193 mg/dL (39%↓). There was no significant difference in mean carotid IMT or in events between the two treatment groups.

The ENHANCE trial was presented at the Annual Scientific Sessions of the American College of Cardiology with virtually no debate. Its publication prompted a committee of the American College of Cardiology to recommend using ezetimibe only as a last resort lipid-lowering agent, with a preference for higher-dose statins, niacin, fibrates, and bile-acid resin before resorting to ezetimibe. This recommendation, in my view, loses sight of the lipid-lowering goal, which is maximal benefit with minimal risk. There is no evidence to date that ezetimibe (approximately 80% not absorbed from the gut) is hazardous. At the lower doses of statins, ezetimibe provides an average 18% further reduction of serum LDL cholesterol, and thus it is a "statin-sparing" drug. And, side effects of statins are dose related: the higher the dose, the greater the potential for side effects. In contrast to the average 18% additional reduction with 10 mg

Table 1. Cardiovascular outcome studies with lipid-lowering agents in the first decade of the 21st century

Study	Year of publication	Journal of publication	Number of subjects	Subjects	Ages (years)	Length of study (years)	Comparison	Events		Relative risk reduction	LDL (mg/dL): mean baseline→end	
								Patients	Controls		Patients	Controls
MIRACL (1)	2001	JAMA	3,086	ACS	Mean 65	0.31	A80 vs P	14.80%	17.40%	↓ 16%	124→72	124→135
HPS (2)	2002	Lancet	20,526	CAD, PVD, Stroke, DM	40–80	5	S40 vs P	7.60%	9.10%	↓ 17%	131→90	131→129
ASCOT-LLA (3)	2003	Lancet	10,305	SH	40–79	Median 3.3*	A10 vs P	1.90%	3.00%	↓ 31%	133→90	133→126
PROVE-IT (4)	2004	NEJM	4,162	ACS	Mean 58	Mean 2	A80 vs Prav 40	19.7%	22.3%	↓ 14%	106→62	106→95
CARDS (5)	2004	Lancet	3,838	DM	40–75	Median 3.9*	A10 vs P	9.4%	13.4%	↓ 37%	117→81	117→120
A–Z (6)	2004	JAMA	4,497	ACS	Mean 61	0.5–2	S40→80 vs P→S20	14.4%	16.7%	↓ 11%†	112→66	111→81
TNT (7)	2005	NEJM	10,001	CAD, PVD, Stroke, DM	Mean 61	Median 4.9	A80 vs A10	8.7%	10.9%	↓ 22%	97→77	98→97
IDEAL (8)	2005	JAMA	8,888	MI	<80	Median 4.8	A80 vs S20	9.3%	10.4%	↓ 11%†	122→81	121→104
SPARCL (9)	2006	NEJM	4,731	Stroke, TIA	Mean 63	Median 4.9	A80 vs P	11.2%	13.1%	↓ 16%	133→43	134→129
SEAS (10)	2008	NEJM	1,873	AS	Mean 67	Median 4.3	S40 + E10 vs P	35.3%	38.2%	↓ 9%†	140→75	139→134
JUPITER (11)	2008	NEJM	17,802	Healthy	Median 66	Median 1.9*	R20 vs P	0.016%	0.028%	↓ 47%	108→55	108→109

A indicates atorvastatin; ACS, acute coronary syndrome; AS, aortic stenosis; CAD, coronary artery disease; DM, diabetes mellitus; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; P, placebo; Prav, pravastatin; PVD, peripheral vascular disease; R, rosuvastatin; S, simvastatin; SH, systemic hypertension; TIA, transient ischemia attack.

*Stopped early; study planned for 5 years.

†Not significant.

Table 2. Imaging studies using statin drugs in the first decade of the 21st century

Study	Year of publication	Journal of publication	Type study	Artery studied	Subjects	Mean age (years)	Length of study (years)	Drug comparison	Plaque change*		Type of patients	LDL (mg/dL): mean baseline→end	
									Patients	Controls		Patients	Controls
ASAP (12)	2001	Lancet	IMT	Carotid	325	30–70	2	A80 vs S40	0.031% ↓	0.036% ↑	FH	309→150	322→187
REVERSAL (13)	2005	NEJM	IVUS	Coronary	502	56	1.5	A80 vs Prav 40	0.2% ↓	5.1% ↑	CAD†	150→79	150→110
ASTROID (14)	2006	JAMA	IVUS	Coronary	349	58	2	R40 vs P	0.98% ↓	—	CAD†	130→61	—
METEOR (15)	2007	JAMA	IMT	Carotid	984	37	2	R40 vs P	0.0014% ↓	0.0131% ↑	Healthy	155→78	154→152
ENHANCE (16)	2008	NEJM	IMT	Carotid	720	48	2	S80 + E10 vs S80	0.0111% ↓	0.0058% ↑	FH	319→141	318→193
SANDS (17)	2008	JAMA	IMT	Carotid	499	56	3	Aggressive vs standard	0.012% ↓	0.038% ↑	DM	104→72	104→104

A indicates atorvastatin; CAD, coronary artery disease; DM, diabetes mellitus; E, ezetimibe; FH, familial hypercholesterolemia; IMT, intimal medial thickness; IVUS, intravascular ultrasonic imaging; LDL, low-density lipoprotein cholesterol; P, placebo; Prav, pravastatin; R, rosuvastatin; S, simvastatin.

*Units are mm^3 for ASAP, REVERSAL, and ASTROID and mm for METEOR, ENHANCE, and SANDS.

†By angiogram.

of ezetimibe, colestipol can also provide an 18% LDL reduction, but it requires 30,000 mg of the drug for the same percent reduction, and cholestyramine at 24,000 mg/day also will give an 18% average LDL reduction. When a 10-mg tablet will give the same LDL reduction as multiple pills amounting to 30,000 mg or 24,000 mg, it is obvious which drug is preferable. Thank you, "expert committee," but I will stay with ezetimibe with its good efficiency and safety, and lack of side effects.

Numerous editorials followed in various medical journals (18–25). Many physicians switched many patients away from Vytorin (the one-pill combination of ezetimibe + simvastatin), and almost certainly the number and percentage of patients lowering LDL cholesterol to <100 or to <70 mg/dL decreased. Maximum benefit was eliminated by a perceived lack of benefit!

Now why was the ENHANCE trial a negative one? There has been considerable public discussion of this point. I believe the difference in the two arms, namely S80 + E10 vs S80, was not great enough in the 2 years of the study to show IMT regression or lack of progression when the IMT of the carotid arteries at baseline was essentially normal. Two preceding carotid IMT trials, each also of 2-year duration, had shown significant difference in the primary endpoints. In ASAP (12), the same patients were studied but the potency difference between the study drug (atorvastatin 80 mg) and the control drug (simvastatin 40) was four times, and in the METEOR trial (15), rosuvastatin 40 mg (its maximal dose) was compared with placebo! In the ENHANCE trial, the potency difference between the study group (S80 + E10) and the control group (S80) was inadequate. If the dose of simvastatin in the control group had been 20 mg or 40 mg, the study may have been a positive one, and then there would not have been such commotion in both the medical and media communities.

On January 8, 2009, the Food and Drug Administration's safety review committee reported that it had completed its review of the ENHANCE trial comparing Vytorin with Zocor and concluded that it supported the continued use of Vytorin (26). Pending results from the IMPROVE-IT trial involving 18,000 patients and expected to be completed in 2012, the agency advised that "based on currently available data, patients should not stop taking Vytorin or other cholesterol-lowering drugs."

A more recent trial—SEAS—showed a slight increase (105 cases vs 70 cases) in cancer during the median 4.3 years of the trial, and that of course led to a safety scare (10). This outcome trial involved patients with valvular aortic stenosis: 333 received S40 + E10 vs placebo. The trial failed to show slowed progression of aortic stenosis in the treatment group and also showed no reduction in events due to the aortic stenosis (although it did show a decrease in myocardial ischemic events). The mean age of patients in this trial was 67 years. Aortic stenosis in this age group is associated with heavy calcific deposits, and it seems unlikely that lipid-lowering at this stage would be beneficial. In contrast, lipid-lowering therapy in a 20-year-old with a bicuspid aortic valve might prove useful in preventing or delaying the development of aortic stenosis. The cancer scare resulting from this trial was of course attributed to ezetimibe, since none of the simvastatin monotherapy trials had shown an increase in cancer. As a consequence, Richard Peto (probably the world's premier statistician) and colleagues (25) compared the incidence of cancer in the SEAS trial of 1873 patients followed a mean of 4.1 years to cancer data from two large ongoing trials: the SHARP trial involving 9264 patients with mean follow-up so far of 2.7 years, and the IMPROVE-IT trial, currently involving 11,353 patients with a mean follow-up so far of 1 year. In SHARP and IMPROVE-IT combined, there was no overall excess of cancer (313 cases in the treatment group vs 326 cases in the control group) and no particular excess of cancer at any particular site. The authors concluded: "The available results from these 3 trials do not provide credible evidence of any adverse effect of ezetimibe on rates of cancer."

The third lipid-lowering trial that has received enormous medical and media editorial attention is the JUPITER outcome trial involving 17,802 apparently healthy men and women (mean age, 66 years, with serum LDL cholesterol <130 mg/dL [mean, 108] and high-sensitivity C-reactive protein ≥2 mg/dL [median, 4.2]) (11). The treatment group received rosuvastatin 20 mg daily (vs placebo). The trial was stopped in 1.9 years (maximal 5). In the treatment group, LDL cholesterol levels were reduced by 50% (to 55 mg/dL) and C-reactive protein levels by 37% (to 1.8 mg/dL). The combined primary endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina pectoris, or death from cardiovascular causes was reduced by 41%, including a 48% reduction in stroke and a 20% reduction in death from any cause. These are spectacular results and indicate that getting the LDL cholesterol into the 50s leads quickly to major reductions in major cardiovascular events and a reduced need for hospitalization or cardiovascular procedures.

But how was the JUPITER trial (published in the *New England Journal of Medicine* on November 20, 2008) received by the media? In an unsigned editorial in *The New York Times* (November 17, 2008) entitled "Who Should Take a Statin?" the author concluded: "Before rushing ahead [and giving several million more people a statin] it will be crucial to establish who might really benefit. . . . The long-term safety of drastically lowering cholesterol levels [must be established] before committing patients who have no clinical signs of disease to decades of drug treatment" (27). Statins have been out in the USA now for 22 years, and this miracle drug—one that actually can and does prevent heart and brain attacks—still is greatly underprescribed and underdosed in millions of people who need it. Statins are the best life insurance against atherosclerotic events ever created, but they are not useful if not taken. Only pure vegetarian-fruit eaters, for practical purposes, do not need it. Most of the rest of us do!

The November 17, 2008, issue of *The New York Times* had a piece entitled "A Call for Caution in the Rush to Statins" by Tara Parker-Pope (28). She suggested "that statins (like Crestor . . . and Lipitor . . .) are far from magic pills. While they clearly save lives in people with a previous heart attack or other serious heart problems, for an otherwise healthy person the potential benefit remains small." Where is she coming from? She goes on:

"And because of the way the JUPITER results were reported, many healthy people are likely to get an exaggerated view of the statin's benefits. While the investigators reported an impressive sounding [her word] 50 percent reduction in the risk of serious heart problems among the statin users, in reality everyone in the study had a low risk to begin with." But they who took the drug got a much lower risk!

And *USA Today* (February 2, 2009) had its say in a piece entitled "That Bad Cholesterol Just Got Worse" by Steve Sternberg (29). The same critical theme followed. Why keep shooting down a miracle? We all—if we continue our present habits—can choose angioplasty and stents or bypass or lower our LDL drastically. I prefer the latter.

US HEALTH

Time magazine in its December 1, 2008, issue had a piece on America's health by Alice Park (30). Some observations:

1. Two thirds of American adults are overweight, and half of them are obese.
2. Most of us pass our health habits to our kids, who may be the first generation of American children who have shorter life spans than their parents.
3. The USA spends 16% of its gross domestic product on health care, far more than any other nation. The next closest is Switzerland, 11%. Japan spends 8%; Russia, India, and China, 5%; and Indonesia, 2%.
4. The annual health care spending per capita in the USA is $7026. France and Canada spend $4000; Britain, $3300; Japan, $2700; and Russia, $369. Of these medical expenses, hospital costs consume 31%; physician and clinical services, 21%; prescription drugs, 10%; nursing home care, 9%; administrative costs, 7%; and other items, 12%. (I believe that these hospital costs are far too low.)
5. Despite spending the most money on health care, life expectancy at birth is lower and infant mortality rates are higher in the USA than in most other developed nations. The highest life expectancy is in Japan, 83 years; Switzerland and Australia, 82; Canada, France, and Italy, 81; Germany and Norway, 80; United Kingdom (UK), 79; and the USA, 78 years. The life expectancy in China is 73 years; Russia, 66; India, 63; Iraq, 56; Nigeria, 48; and Afghanistan, 42. Infant mortality rates per 1000 live births are lowest in Singapore, 2; Japan, 3; France, 4; UK and Canada, 5; and USA, 7. Russia is 12; China, 20; India, 57; and Afghanistan, 165.
6. The percentage of adults who smoke in Greece is 52%; Russia, 49%; UK, 36%; Spain, 34%; China, 32%; Germany, 32%; Japan, 30%; Sweden, 22%; and USA, 20%.
7. The frequency of hypercholesterolemia, the heart disease death rate, the rate of new cases of cancer diagnosed each year, the percentage of patients with cancer dying within 5 years, and the rate of stroke are all decreasing. Death from cardiovascular disease per 100,000 people yearly in Japan is 106; France, 118; Spain, 137; Canada, 141; UK, 162; USA, 188; Germany, 211; Cuba, 215; China, 291; and Iraq, 508.
8. Forty percent of Americans get no exercise, 30% get some exercise, and 31% get regular exercise.
9. Tens of thousands of people in the USA die each year because they lack access to timely and effective health care. Fifteen percent of the population is uninsured, including 25% of Texans. Physicians are scarce in many rural areas of the USA, and that scarcity is greater in 2007 than it was in 1987.

In my view, health will improve in the USA only when each of us takes full responsibility for our health, and that starts when we pull our chair up to the table 21 times a week. As Dr. Caldwell Esselstyn said, "Food trumps everything," and that goes for both atherosclerosis and our most common cancers.

20TH-CENTURY GENOCIDE

In 2002 there appeared a book entitled *The New Killing Fields: Massacre and the Politics of Intervention,* edited by Nicolaus Mills and Kira Brunner (31). The book provides detailed observations on the killers and those killed in 10 civilian massacres occurring in the 20th century, and they are briefly summarized in *Table 3.* In her chapter, Samantha Power (32) indicated that Raphael Lemkin, a Polish jurist who lost 49 members of his family in the Holocaust, invented the word *genocide* in 1944. Prior to Lemkin's coinage, the systematic targeting of national, ethnic, or religious groups was known as *barbarity*. In 1948, largely on Lemkin's prodding, the United Nations (UN) General Assembly unanimously passed the UN's first ever human rights treaty, the Genocide Convention, which required signatories "to

Table 3. 20th-century genocides*

	Year	Killer	Target group	Number killed (millions)
1	1915	Turkey	Armenians	1.0
2	1939–1945	Germany	Jews Poles Roma Homosexuals Political opponents	6.0 5.0
3	1969	Nigeria	Ibos of Biafra	
4	1971	Pakistan	Bengali	>1.0
5	1972	Burundi (Tutsi)	Hutu	0.1
6	1975–1979	Cambodia (Khmer Rouge or Red Khmer)	Their own	2.0 (of the country's 7 million)
7	1975–1999	Indonesia (anti-independence)	East Timor (pro-independence population)	0.5–1.0
8	1987–1988	Iraq	Kurds	>0.1
9	1992	Bosnian Serbs	Bosnian Muslims and Croats	0.25
10	1994 (100 days)	Rwanda Radical Hutu	Rwanda Tutsi and moderate Hutu	0.80 (of the country's 8 million)

*Compiled from Mills and Brunner (31).

undertake to prevent and punish" genocide. Unfortunately, the convention's language was vague on precisely how the UN member states would meet their obligations, making no mention of military intervention and trusting that domestic prosecution of future "genocidists" would deter massacres.

Few of the genocidists in the 20th century, except for a few of the Nazis, have been prosecuted. Before the Holocaust, neither the US nor European diplomats uttered much protest when Germany passed the Nuremberg Laws and began destroying Jewish businesses, synagogues, and homes. Britain and France went to war with Germany after Hitler invaded Poland in September 1939. President Franklin Roosevelt kept America neutral until after the Japanese attack on Pearl Harbor and after Adolph Hitler declared war on the USA. The Allies did nothing directly aimed at ending the Nazis' extermination of the Jews.

What is most shocking about the reaction of what Lemkin called the "civilized world" to the 20th-century genocides is that they did virtually nothing to deter the crimes. Because their "vital national interest" was not considered imperiled by the genocide, military intervention rarely was even considered. Most Western states adopted a "policy of silence." The Western powers did not merely do nothing but on occasion they directly or indirectly aided those committing the genocide. For example, through the 1980s, the USA orchestrated the vote at the UN to favor maintaining recognition of the Khmer Rouge. The Western powers sided with and supplied credit, military intelligence, and arms to Iraq while Hussein was killing the Kurds in Northern Iraq. The major powers on the UN Security Council used their clout to mandate the withdrawal of the UN peacekeepers from Rwanda and to block the deployment of reinforcements. The USA maintained an arms embargo against the Bosnian Muslims even after it was clear that the arms band prevented the Muslims from defending themselves.

Nearly a century after the "race murder" of the Armenians and more than a half century after the liberation of the Nazi death camps, the question remains as to why decent men and women who firmly believe that genocide should "never again" be permitted allow it to happen. The often-quoted response is "we didn't know" or "we didn't fully appreciate," but these answers are not credible. The main reason American leaders turn away is that genocide in distant lands has not captivated American senators, congressional caucuses, Washington lobbyists, elite opinion shapers, grassroots groups, and individual constituents. As a result of this society-wide silence, government officials have calculated that the political cost of getting involved in genocide prevention has far exceeded the cost of remaining uninvolved. Bosnia was the only genocide of the 20th century that was eventually met with a military response! The reason in that case was intense domestic pressure.

The September 11, 2001, attacks on the Twin Towers in New York City may have permanently altered US foreign policy toward genocide. The fanatics who targeted civilians in New York City did so simply because of who they were, namely Americans. To earn a death sentence in the last century, it was enough to be an Armenian, a Jew, or a Tutsi. On September 11, it was enough simply to be an American. In 1994, Rwanda, a country of 8 million, experienced the equivalent of more than two World Trade Center attacks every day for 100 days! This was the equivalent of 230,000 Americans killed each day, or 23 million Americans murdered in 3 months. When, on December 12, 2001, the USA turned for help to its allies, Americans were gratified by the overwhelming response. When the Tutsi capital cried out, by contrast, every country in the world turned away.

For the foreseeable future, suggests Ms. Power, American leadership will be necessary to stop or punish genocide. The USA does not have the resources, of course, to simultaneously defend itself from attack and deploy its troops to every trouble spot where the threat of ethnic violence lurks. But US policy need not be framed in terms of doing nothing or sending in the troops. There will be times when US intervention will be inappropriate and times when the risk to US soldiers will outweigh the benefits a military intervention would likely bring to the victims. Just because the USA does not deploy its troops does not mean that a US leadership role is not required or that other forms of intervention should not be tried. Calling genocide something it is not—"civil war" or "tribal violence"—to mute public pressure is dishonest and detrimental to sound policy, as Samantha Power indicates. Handling atrocity as war leads to the deployment of conflict resolution experts, the misguided pursuit of cease fires, and the spiraling investment in "peace processes" that too often become stalling devices that shield murder. Power suggests that we need to respond not as an all-or-nothing proposition but by publicly identifying and threatening the perpetrators with prosecution, demanding the expulsion of representatives of genocidal regimes from international institutions, closing the perpetrators' embassies in Western capitals, and calling upon countries aligned with the perpetrators to use their influence. Establishing economic sanctions, freezing foreign assets, or imposing an arms embargo are other useful endeavors.

Physicians treat one patient at a time, but maybe we should use our influence more to save thousands of lives at a time.

REDUCING FLAWS IN THE REVIEW PROCESS OF MANUSCRIPTS SUBMITTED TO MEDICAL JOURNALS FOR PUBLICATION*

Before speaking on the assigned topic, let me briefly provide my qualifications for doing so. I became editor of *The American Journal of Cardiology* (AJC) in June 1982. From 1983 through 2008, 58,282 manuscripts passed across my desk and 17,979 were accepted. In 1982, just over 1100 manuscripts were submitted; in 2007, nearly 3200. Additionally, I have authored over 1000 publications in peer-reviewed journals. Being on the author's end has taught me more than being on the editor's end.

Before providing suggestions to reduce flaws in the review process, let me mention some advantages and disadvantages of the process. First, some *advantages*: Clearly, the review process improves the reporting of medical science and in this way is useful to authors, to editors, to reviewers themselves, and

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consequently to patients. Most reviewers are impartial and most are good at detecting inconsistencies, incongruities, omissions, commissions, and inadvertent errors; inadequate descriptions or characterizations of the populations studied; improper study designs; outdated methods; poor figures and tables; inappropriate or exaggerated conclusions; and poor syntax. Correction of these deficiencies obviously improves manuscripts. Reviewing a manuscript makes the reviewer read more critically than he or she might do otherwise; it thus improves his or her own database and theoretically makes him or her a better investigator, teacher, and physician. Another infrequently mentioned advantage of the review process is that it makes authors more careful in their preparation of manuscripts because they need to "cover their flanks," so to speak, to persuade both reviewers and editors that their manuscript is of high quality. And reviewers also provide "ammunition" for editors, making the declining of manuscripts, particularly ones from a very prominent investigator or friend, a bit easier.

Now to *disadvantages*: The review process, of course, is time consuming, expensive, and delays publication; is often biased; is relatively poor in detecting plagiarism, deceit, and intentional errors (fraud); and, on occasion, offers suggestions, which, if carried out, do not improve the scientific quality or the readability of the manuscript. Manuscripts tend to be reviewed by investigators involved in the same type of research. The reviewers, in other words, are often scientific competitors. (The process is like asking Ford to review plans for a new car design by General Motors without compensation.) Not all reviewers are experts in the subject of the manuscript they are asked to review. The process also can exhaust the better reviewers. And the worst manuscripts usually get the most reviews because they move from one rejection to another until they are finally accepted by some journal for publication.

Now to suggestions, directed mostly to editors, for reducing flaws in the review process:

1. Give careful thought to who would be the best reviewers of a manuscript. The expertise of the review is dependent on the expertise of the reviewer.
2. Ask authors to give names of potential out-of-city reviewers whom they believe will provide nonbiased critical reviews of their work. Editors have no monopoly on the correct picking of reviewers! Reviews and recommendations by reviewers suggested by authors are usually relatively similar to those suggested by editors.
3. Ask authors to also give the names of potential out-of-city reviewers whom they believe will provide a biased (unfair) review of their work and do not send their manuscript to those individuals.
4. Refrain from sending many manuscripts to hypercritical potential reviewers where no manuscript or work (other than their own) is quite good enough. Likewise, reviewers with obvious conflicts of interest or those who abuse the review process (acquiring ideas or protecting their own investigations) should be avoided.
5. Don't overwork the exceptional reviewers. These particularly helpful reviewers tend to review for multiple journals, and their energies can be depleted by excessive reviewing. Consider saving them for potentially controversial manuscripts.
6. Refrain from regularly sending manuscripts that initially receive mixed recommendations to third reviewers. At times I have exchanged the positive and negative reviews between initial reviewers with advantage to all parties before returning the manuscript to the author. Discussion of these manuscripts with associate editors also saves additional reviews.
7. Compose the editorial board in a meritorious fashion, so that it consists of individuals proven to be conscientious and prompt reviewers and not just prominent investigators or chiefs of prominent departments or divisions.
8. Refrain from sending some types of manuscripts for review or at least have no requirement that all submissions be sent for outside review. For example, some editorials, readers' comments, reviews, debates, symposia, and case reports may not need to be reviewed.
9. Don't substitute reviewers for editors. All manuscripts need the editor in chief's opinion. Authors deserve it. I edit originally submitted manuscripts before returning them to authors for their revisions.
10. Refrain, except in unusual circumstances, from sending revised manuscripts back to one or more reviewers of the originally submitted manuscript for reevaluation. If this is to be done, I inform authors when returning to them the originally submitted manuscript.
11. Decline extremely poor manuscripts without outside review, thus saving the time and energy of reviewers for more worthwhile manuscripts.
12. Reduce the reviewing of manuscripts previously declined by another journal by asking authors to submit the previous reviews and responses to them, the manuscript originally sent to the other journal that declined the manuscript, and the revised manuscript to the new journal. This option has been used by the AJC since 1982, and it usually prevents the necessity of starting the review process anew.
13. Remember the golden rule of reviewing. The frequent author is usually a frequent reviewer, but the two hats are worn at different times. When authors submit manuscripts to a journal, their patience for delay in receiving the "acceptance" or "rejection" decision often is short. When these same authors, however, become reviewers, their patience for delay often appears to be much longer. Reviewers need to treat authors as they would like to be treated when they are authors.
14. Handle the review process online. Online peer review improves efficiency: reviews are returned more quickly and authors receive decisions more quickly than when transferring paper.
15. Forget blind reviewing, whereby the names and institutions of the authors are not supplied to the reviewers. This system was tried at the AJC for 6 months, and a few reviewers resented not knowing for sure the names of the

authors of the manuscripts they were asked to review. On the other hand, giving authors the option of requesting blind reviews and giving reviewers the option of signing their reviews are reasonable and improve the transparency of the process.

16. Keep the final decision on manuscripts in the hands of the editor in chief. Reviewers serve to provide suggestions to both authors and editors on means to improve the quality of manuscripts. Reviewers should not replace editors, whose charge is to decide, among other things, which manuscripts to accept and which to decline, and, if acceptable, in what form.
17. Continuously update the reviewer files. Periodically ask editorial board members, among others, for names to be added to the journal's reviewer file. Get investigators involved in the reviewing of manuscripts early in their careers. The young are often more critical than the old, and they generally have more time to do the review.
18. Emphasize to authors the importance of following the journal's instructions to authors. Study the journal's format before submitting the manuscript. An editor's patience can be tested by not doing so. And if a manuscript is declined by one journal, make sure that the previous reviewers' comments are responded to by altering the manuscript before sending it to the next journal. Not doing so is an insult to the review process.
19. Befriend the publisher. Work in parallel as much as possible. Minimize surprises on both sides. The process works smoother when there is a friendly relationship between editor and publisher.
20. Before sending a manuscript to a journal, have a local fellow investigator—a friend—examine the work. Others can see in our manuscripts oversights that can be corrected before submission to a journal.
21. Remember that peer review also follows publication through readers' comments (letters to the editor) and other discussions (such as journal clubs, medical meetings, media).
22. Thank reviewers for particularly outstanding reviews. Occasionally publish their reviews alongside the manuscript. Recognize reviewers in the journal.

In summary, as many have pointed out, peer review is imperfect, being subjective, frequently biased, and unreliable in detecting many imperfections or even fraud, but, nevertheless, the review process improves most manuscripts and there is no substitute for it. Reviewing the manuscripts of others is unselfish, honorable, altruistic, and poorly rewarded, but it is absolutely essential to keep the reporting of scientific investigations to high standards. All of us benefit by having others make suggestions for improving our manuscripts.

THE ANATOMY OF DECEPTION

For Christmas 2008, my daughter, Fran, gave me a book with the above title by Lawrence Goldstone (33). This "mesmerizing forensic thriller thrusts the reader into the operating room, drawing rooms, and back alleys of 1889 Philadelphia." As a young trainee with Dr. William Osler at The Johns Hopkins Hospital, Dr. Ephraim Carroll grapples with solving the murder of a Philadelphia socialite, who is first seen as a corpse in the morgue of Philadelphia General Hospital by William Osler and his trainees. Dr. Carroll believes that he knows the identity of the beautiful young woman. A second mysterious death, determined to have been a ruthless murder, prompts Dr. Carroll to investigate on his own. As he faces a wealthy, seductive woman who clouds his vision and a controversial artist sowing scandal, the secrets of Dr. William Halsted and his protector, Dr. William Osler, begin to unravel before him. The book, however, displays both Osler and Halsted falsely, but fortunately the author freely admits that fact in his "author's note." I just hope that all readers take the time to read the author's note. It is a good read.

READING

According to David Ulin, reading is on the rise. In January 2009, the National Endowment for the Arts (NEA) disclosed that literary reading among adult Americans had increased 3.5% during the last 6 years (34). Its last reading survey in 2002 disclosed a drop in literary reading from its 1992 survey: adult readers fell from 54% to 47% of the population. But what did the NEA mean by "literary" reading? That was defined as "novels and short stories, plays or poems"—in other words, nonfiction was left out entirely. By that definition, I read very little. The 2002 survey disclosed that 96 million Americans were literary readers. That's pretty good. Reading rates, not surprisingly, increased with the level of education: 68% of college graduates, 39% of high school graduates, and 18% of those who never went to high school were "literary readers." Ethnicity was a factor also: 55% of white, 43% of blacks, and 32% of Hispanics met the NEA's "literary reader" definition. Since I am a nonfiction guy, I flunked the "literary reader" definition.

BIRTH WEIGHT AND DIABETES MELLITUS (TYPE 2)

A 35-author report appeared in the December 24/31, 2008, issue of *JAMA* indicating that the lower the birth weight, the greater the chance of developing diabetes mellitus in adulthood (35). (When I was in medical school, I was taught the very opposite.) I don't recall seeing an article before with 35 authors.

GLUCOSE CONTROL AND VASCULAR COMPLICATIONS IN DIABETES MELLITUS

I was also taught in medical school that the better the blood glucose is controlled in patients with diabetes, the fewer the complications. That too has proved to be wrong. Duckworth and colleagues (36) studied 1791 military veterans and divided them into two groups: one group received intensive glucose control and the other, standard glucose control. After following these patients an average of 5.6 years, the group who had their blood glucose intensively controlled had the same rates of major cardiovascular events, death, or microvascular complications during the period of this study. Another "principle" has been overturned.

BIRDS AND PLANES

The recent emergency landing of a commercial aircraft in the Hudson River prompted the Federal Aviation Administration and the Department of Agriculture to release a study of bird strikes to civil aircraft from 1990 to 2007 (37). The study analyzed 73,669 known strikes to commercial aircraft. The bird strikes hit different areas of the plane: windshield, 17%; engine, 15%; nose, 14%, wing/rotor, 13%; fuselage, 13%; radome, 12%; and other, 17%. The strikes most commonly occurred during the takeoff run or climb (37%) or during the approach or landing (55%). The strikes had no effect 87% of the time but did lead to precautionary landings in 7% or abortive takeoffs in 3%. Engine shutdowns fortunately occurred in only 1%.

COMMERCIAL AIRLINE SAFETY

No passengers died in commercial airline crashes in either 2007 or 2008, a period in which commercial airliners carried 1.5 billion passengers on scheduled airline flights (38). One major accident occurred during that time, the December 2008 crash of a Continental Airlines jet in Denver. Only 4 years since 1958 have passed without a passenger fatality, much less a 2-year period. Arnold Barnett, a Massachusetts Institute of Technology professor who has written extensively about airline fatality risks, calculated that it was more likely for a young child to be elected president in his or her lifetime than to die on a single jet flight in the USA or similar industrial nation in Europe, Canada, or Japan. Fatality risk fell to 68 per billion fliers in the present decade, less than half the risk in the 1990s, according to the National Transportation Safety Board.

SURVIVING

In January 2009 the book *The Survivor's Club: The Secrets and Science that Could Save Your Life* by Ben Sherwood appeared (39). Here are some of his recommendations. The safest seats on an airplane are within five rows of any exit. The safest seats are in an exit row or one row away. When staying in a hotel, pick a room on or below the seventh floor. The reason is that most fire departments use ladders that at their maximum can extend around 80 feet into the air. It is impossible to climb out of a building's window and onto a truck's ladder if you are above the seventh floor. More patients die from serious illnesses if they are admitted to hospitals on weekends rather than during the week. Additionally, try not to check out of hospitals on a Friday, the most common hospital discharge day; those discharged on that day have an increased risk of death or readmission to the hospital within 30 days. The best place to have a cardiac arrest is in a casino in Las Vegas. In Vegas, security cameras and guards constantly scan the casino floors to catch cheaters, thieves, and troublemakers. If a visitor collapses, someone will notice right away. Security personnel are trained in the use of defibrillators and usually can administer the life-saving shocks within 2 or 3 minutes. Heart attack survival rates in Las Vegas are 53% compared with 16% in Seattle and 2% in Chicago. The safest seat in an automobile is on the hump of the back seat, which is 25% safer than riding in the rear window seat. The safest car color is white, not dark. According to a 17-year study of automobile crashes in Australia that resulted in death, injury, or serious damage, the researchers found that white cars were less likely to be involved in accidents than those of any other color. Compared with white cars in daylight hours, black cars have a 12% higher crash risk; gray, 11%; silver, 10%; blue and red, 7%. At dawn or dusk, black cars had a 47% higher crash risk than white cars; gray, 25%; and silver, 15%. The three deadliest days for pedestrians are January 1, December 23, and October 31. Women are more likely to die in the week after their birthdays than any other week of the year, while men's deaths peak just before their birthdays.

EARTHQUAKES IN 2008

The US Geological Survey estimated that several million earthquakes occur worldwide each year, but most are too small or too remote to be detected. Location and depth as well as the seismic stability of buildings and roads determine how much damage they do. In 2008, earthquakes killed 88,070 people—the highest figure since 2004. In 2008, killer quakes hit 14 countries on four continents, including China, Algeria, Columbia, Democratic Republic of the Congo, Greece, India, Indonesia, Iran, Japan, Kyrgyzstan, Pakistan, Peru, Russia, and Rwanda (40). The year's strongest quake was in Sichuan, China, on May 12. At least 69,185 people were killed, 18,467 left missing and presumed dead, and 374,171 injured from the 7.9-magnitude quake. The deadliest year for earthquakes since the 1970s was 2004, when tsunami waves generated by an undersea earthquake near Indonesia killed nearly 229,000 people. The deadliest quake in the past 4 centuries was on August 7, 1976, in Tangshan, China, with an estimated toll of about 655,000 persons.

US BIRTHS

According to figures for 2005 compiled by the Centers for Disease Control and Prevention, 4 million babies are born in the USA each year. August is the busiest month for births, and February is the slowest month; Tuesday is the busiest day, and Sunday is the slowest day (41). Utah has the highest birth rate and Vermont, the lowest birth rate. The average age of first-time moms in the USA now is 25 years.

DEBTS OF MEDICAL SCHOOL GRADUATES IN 2008

Approximately 13,400 medical students responded to the 2008 questionnaire: 18% had educational loans of ≥$200,000 (vs 5% with that amount of debt in 2004), and 9% of graduates had debt levels between $175,000 and $199,000 (42). The average debt load of the 2008 graduates was $141,751, more than $10,000 higher than the 2007 graduates. And then there are 4-plus years of post-graduate training where the income barely covers living expenses.

DEEP THROAT

It was *Mark Felt,* who died at age 95 in December 2008 (43). He of course was the crucial source of the Watergate stories by Washington reporters Bob Woodward and Karl Bernstein that led to President Nixon's resignation. Deep Throat appears to be the most famous anonymous source in history, and there was

much speculation about the source until 2005 when Mr. Felt, who had been No. 2 in the FBI during Nixon's last years, outed himself. Although Mr. Felt described the various unconstitutional excesses of Nixon's presidency, Mr. Felt was not so clean himself. He had authorized illegal break-ins as an FBI honcho and was convicted of conspiring to violate constitutional rights of American citizens in 1980. In a weird twist, Mr. Nixon testified on his behalf. Like Nixon, Mr. Felt received a presidential pardon for his crime. Although Deep Throat was of course useful in exposing the Nixon administration's excesses, the use of anonymous sources damaged journalism's credibility after Watergate and possibly harmed our democracy.

HUMAN LITTER

In January 2009, Nadia Suleman—33 years old, unmarried, unemployed, and already the mother of six—delivered eight babies weighing from 1 pound 8 ounces to 3 pounds 4 ounces in 5 minutes (44–46). All 14 apparently were conceived by in vitro fertilization. Ms. Suleman recently filed for bankruptcy. It appears that Ms. Suleman was implanted with six embryos left over from her earlier treatments. It is against all guidelines to implant more than two embryos in a woman under age 35. Her new babies will cost at least $1 million in neonatal care, more if they have the typical range of disabilities for premature babies. So, it's infertility treatment for an unemployed, single mother of six and eight embryos in one womb. As Ellen Goodman says, "It is nuts."

TATTOOS

Dr. Bernadine Healy, a former fellow of mine when I was at the National Heart, Lung, and Blood Institute in Bethesda, Maryland, had a piece in the *U.S. News & World Report* on tattoos (47). She indicated that as many as half of those who get tattoos later wish they hadn't. The cost of getting a tattoo may be in the hundreds of dollars, but removing them can run into the thousands. Seven facts about tattoos. 1) There is limited oversight of the tattoo industry. The Food and Drug Administration, which regulates food, cosmetics, and drugs, does not regulate the tattoo world, even though it warns that many health risks come from this procedure. 2) Ingredients of tattoo ink are a mystery. Some contain mercury, lead, and antifreeze. 3) Removal of tattoos is a major and painful excavation in which pigments are either surgically excised or attacked with a laser. 4) The lasers' intense heat not only breaks up the ink's pigment crystals but also triggers chemical reactions that generate carcinogens and other hazardous chemicals that are absorbed by the body. 5) People become unhappy with their tattoos because of a desire to separate from the past, embarrassment, and/or fears that tattoos might adversely affect their job or career. 6) Women suffer psychological distress and tattoo stigma more than men do. I am not a tattoo man and think the human body is prettier without them.

TAXING COKES

According to Nicholas Kristof (48), it was the cigarette tax that caused so many people to quit smoking. Every 10% price increase on cigarettes reduced sales by about 3% overall and 7% among teenagers. According to the 2005 book *Prescription for a Healthy Nation,* the author calculated that the 1983 increase in the federal tax on cigarettes subsequently saved 40,000 lives per year. Now, New York Governor David Patterson has proposed an 18% sales tax on soft drinks and other nondiet sugary beverages, a proposal that would raise $400 million a year for the state. The average American consumes about 35 gallons of nondiet soda each year and gets far more added sugar from soda than from desserts. Tax the stuff!

—William Clifford Roberts, MD
12 February 2009

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